Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

127

Hepatobiliary Disease

JOHANNA P. DAILY
JAMES H. MAGUIRE

INTRODUCTION

The hepatobiliary tract is the target of a wide variety of tropical infections. Some diseases, such as chronic hepatitis and biliary ascariasis, are important causes of morbidity and mortality among residents of the tropics in many parts of the world. Others, such as hepatitis A, pose a greater threat to the expatriate traveler. Among the millions of persons in the tropics with the acquired immunodeficiency syndrome (AIDS), opportunistic infections with even once obscure pathogens have become important causes of hepatobiliary disease.

DIAGNOSTIC CONSIDERATIONS

For patients with known or suspected hepatobiliary disease, categorizing the problem into one of several clinical syndromes narrows the list of diagnostic possibilities. Hence, the first step is to determine whether there is parenchymal disease of the liver (hepatitis, cirrhosis, granulomatous and other infiltrative processes, space-occupying lesions), biliary disease (biliary obstruction, other causes of jaundice), vascular disease, or splenomegaly. Priority should be given to life-threatening but treatable conditions such as hepatic abscess, cholangitis, and falciparum malaria, and to diseases that threaten the public health, such as hepatitis A and several of the viral hemorrhagic fevers. It is important to rule out diseases that are also common in temperate climates, such as cholecystitis and pancreatic carcinoma, and noninfectious processes that occur more frequently in the tropics, such as veno-occlusive disease.

The spectrum of hepatobiliary infections differs among residents of the developing world, immigrants from these areas, and the expatriate traveler.[1–9] Acute hepatitis A is common among travelers returning to temperate zones, who typically lack prior exposure and immunity, while it is rare among immigrants and adult residents of the tropics, who experienced infection during childhood.[10] Biliary ascariasis is familiar to clinicians in the developing world, where a large proportion of the population harbors adult worms (see Chapter 109).[11–14] Although ascariasis is not uncommon among immigrants from the tropics, the risk of hepatobiliary complications decreases rapidly during the first year after arrival, because the worms die and are not replaced.

Routine evaluation of the patient begins with a clinical history that may help distinguish between disease processes and point to a diagnosis. There should be questions about the pace of illness, right upper quadrant pain or discomfort, indigestion, jaundice, dark urine, pruritus, fever, anorexia, and other constitutional symptoms. A history of underlying conditions, medications, vaccinations, and an epidemiological history of exposures should be taken. Examination should evaluate the size, consistency, and tenderness of the liver, spleen, and gallbladder. The presence of jaundice, ascites, dilated periumbilical veins, spider angiomata, or other stigmata of liver disease should be ascertained. Measurements of serum bilirubin, liver enzymes, and alkaline phosphatase are part of routine screening for hepatobiliary disease. Depending on their availability, further studies such as measurements of serum albumin and prothrombin time, serologic tests, imaging studies, cholangiography, and liver biopsy may be indicated.

Ultrasonography (US) is more widely available in tropical areas than computed tomography (CT) or magnetic resonance imaging (MRI). US is useful for detecting gallstones, dilated biliary ducts, thickened gallbladder walls, masses within and around the liver, periportal fibrosis, hepatosplenomegaly, and evidence of portal hypertension. US can distinguish solid lesions from abscesses and cysts and can demonstrate certain helminths within the hepatobiliary tree.[15–17]

In the sections to follow, diseases of the hepatobiliary tree are discussed according to clinical syndromes and manifestations. Emphasis is on differential diagnosis and the approach to diagnosis.

ACUTE HEPATITIS

The clinical spectrum of acute hepatitis ranges from asymptomatic illness to fulminant, massive hepatic necrosis. In typical symptomatic cases, there is vague discomfort and tenderness in the right upper quadrant, nausea, anorexia, jaundice, and fever. The broad differential diagnosis is outlined in Figure 127-1. In all cases, a history of exposure to toxins and drugs that cause damage to the liver should be sought.

Elevation of hepatic enzymes and bilirubin also occurs in response to a number of systemic infections, including bacterial sepsis, pneumonia, typhoid fever, and malaria, even when the pathogen does not directly infect liver tissue.[1,18] Cholestasis and frank jaundice are prominent in such cases and may take days to several weeks to resolve after the responsible infection is cleared. In malaria, hepatomegaly without evidence of hepatocellular injury can occur as a consequence of vascular congestion and Kupffer cell hyperplasia.

The most common causes of hepatitis throughout the world are hepatitis viruses A through E (see Chapter 64). In many developing regions, hepatitis A virus (HAV) infection occurs in the first years of life through fecal-oral transmission and is usually asymptomatic.[19] In areas where the quality of drinking water has improved, however, the prevalence of hepatitis A in children has decreased in recent years.[20] Hepatitis A infection is one of the most common causes of illness among travelers to the tropics, occurring at a rate of 3 to 6 per 1000 persons per month in one study and accounting for 60% of cases of hepatitis in returning travelers.[21] Appropriate use of hepatitis A vaccine or pooled serum immunoglobulin reduces the risk of infection among travelers to less than 5% and 15%, respectively.[22]

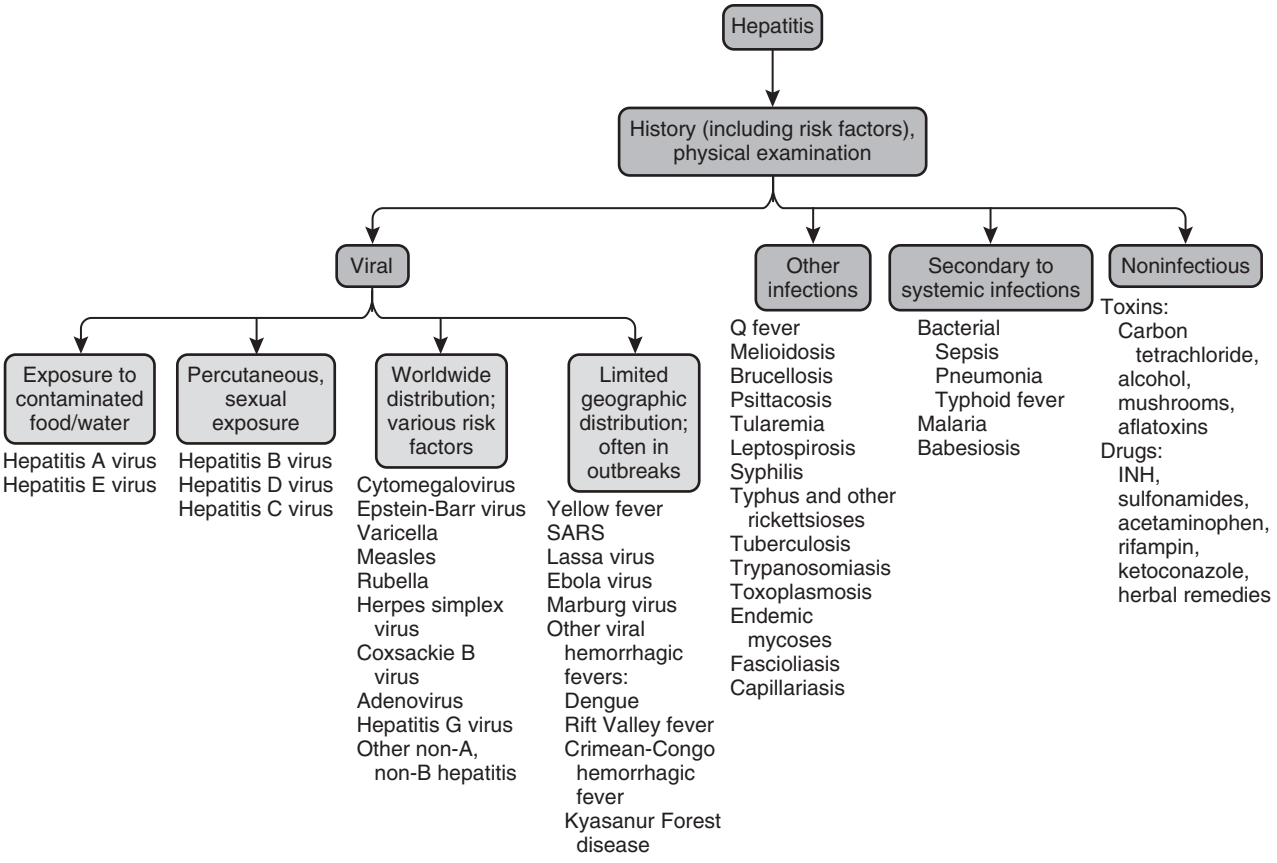

FIGURE 127-1 Differential diagnosis of acute hepatitis.

The prevalence of hepatitis B surface antigenemia varies from less than 1% in Mexico and temperate South America to as high as 15% in parts of Africa, Southeast Asia, China, the Philippines, Pacific islands, Middle East, and the Amazon basin.[23,24] Residents of such areas generally acquire asymptomatic infections in the perinatal and early childhood periods. Acute hepatitis B is four to five times less common than hepatitis A among travelers to the tropics.[25] Expatriates at high risk for hepatitis B include health-care professionals, persons receiving inoculations or dental treatment, and those who engage in unprotected sexual contact or share needles.[26] Only persons infected with hepatitis B virus (HBV) are at risk for superinfection with delta virus (hepatitis D virus, HDV). Direct person-to-person contact of HDV has been responsible for the high number of cases of fulminant hepatitis in the Amazon region (Lábrea hepatitis), northern Colombia (hepatitis of the Sierra Nevada of Santa Marta), and remote Amerindian settlements in Venezuela, rather than percutaneous needle exposure, which is the usual route in other parts of the world.[27–29]

Acute hepatitis C virus (HCV) infection occurs usually via the parenteral route, or less commonly via sexual transmission. It is endemic worldwide with high prevalence in Japan and the Mediterranean countries of Europe, Africa, and the Middle East, where it causes significant morbidity, but is rare among returning travelers.[30–32] High rates of hepatitis C infection in Egypt are attributed to use of inadequately sterilized needles for administration of tartar emetic during mass treatment campaigns to control schistosomiasis in the 1960s through the 1980s.[33] Another virus transmitted via the fecal-oral route, hepatitis E, has caused outbreaks in India, Nepal, Pakistan, the former Soviet Union; parts of Africa, Mexico, and China; and the Middle East. Sporadic cases have been reported among travelers.[34–36]

Distinguishing the different types of hepatitis on clinical grounds alone is difficult. The incubation periods of hepatitis A and B are 2 to 6 weeks and 6 weeks to 6 months, respectively. The hepatic manifestations of HBV infection may be preceded by rash, arthralgia, and arthritis. Mortality due to fulminant hepatitis occurs in 0.15% of persons with HAV infection (and in 2% to 3% of those over the age of 40 years), in fewer than 1% of those with HBV infection, in up to 50% of those with HDV co-infection, and in up to 20% of pregnant women during the third trimester who become infected with hepatitis E virus (HEV).

There are specific immunoglobulin M (IgM) antibody tests for hepatitis A, D, and E. Acute hepatitis B is diagnosed using assays for hepatitis B surface antigen or anti-HBV core antigen.[37,38] Diagnosis of acute hepatitis C requires detection of HCV RNA, since anti-HCV antibodies are usually slow to develop. Household contacts of patients with hepatitis A should receive serum immunoglobulin, and precautions to prevent enteric spread should be taken. Hepatitis B immune globulin and immunization are effective in preventing infection of sexual partners and neonates born to infected mothers.

Other viruses that cause acute hepatitis are listed in Figure 127-1.[39] Diagnosis is made by serologic tests, microscopic examination of biopsy specimens, and viral cultures of liver tissue, blood, urine, and other fluids. In the forested areas of sub-Saharan Africa and South America, yellow fever occurs in epidemics or as sporadic cases among unvaccinated persons, including the occasional traveler (see Chapter 71). Only 10% to 20% of cases of infection with the yellow fever virus lead to the classic syndrome of biphasic fever, jaundice, hemorrhage, and hepatic necrosis. Other agents of viral hemorrhagic fever that involve the liver include the tick-borne Kyasanur Forest disease in India and Crimean-Congo hemorrhagic fever in Africa and Asia; Lassa fever in West Africa; Marburg virus disease in Uganda, Kenya, and Zimbabwe; and Ebola virus disease in Zaire and Sudan (see Chapters 65–67, and 70).[40] Because transmission of the highly lethal Lassa fever, Marburg, and Ebola viruses is by direct contact with blood and excreta, strict isolation and infection control precautions are indicated. Hepatic necrosis has been reported also with dengue hemorrhagic fever and Rift Valley fever. Hepatic impairment and elevated levels of transaminases in the serum that occur in up to 60% of persons with the severe acute respiratory syndrome (SARS) are due to infection of the liver with the SARS-associated coronavirus.[41]

Hepatomegaly and, at times, clinically apparent hepatitis are seen in nonviral infections such as leptospirosis, relapsing fever, and early syphilis (see Chapters 44–46). Hepatitis is rare in Lyme borreliosis. In leptospirosis, the elevation of serum bilirubin is usually out of proportion to that of the hepatic enzymes. Leptospirosis is enzoonotic throughout the tropics, and outbreaks among residents and travelers in the tropics have followed contact with contaminated water or moist soil.[42,43]

Pulmonary involvement and a history of contact with livestock or parturient cats clinically distinguishes the hepatitis of acute Q fever from that of viral hepatitis. Hepatomegaly or hepatitis occurs frequently in typhoid fever, acute brucellosis, tularemia, meloidosis, and psittacosis, as well as in rickettsioses.[44,45] Massive hepatic necrosis may complicate miliary tuberculosis.[46]

A mild increase in serum transaminases can be seen in cases of acute acquired toxoplasmosis. Mild hepatomegaly during acute Chagas' disease results from infection of hepatocytes and Kupffer cells and the host's immune response (see Chapter 93). Approximately 2 months after ingestion of watercress containing metacercariae of *Fasciola hepatica,* immature flukes migrate through the liver, causing right upper quadrant pain, nausea, and fever (see Chapter 117). Tender hepatomegaly and elevated serum hepatic enzymes are suggestive of viral hepatitis, but a marked peripheral blood eosinophilia and urticarial eruptions point to the proper diagnosis. Hypoechoic and hypodense lesions of the liver detected by US and CT correspond to the track of the parasite as it burrows through the liver.[16,47] Diagnosis of acute fascioliasis is made by serologic tests because symptoms precede egg-laying by weeks.[48] Rare human cases of *Capillaria hepatica* have been reported from Africa, Asia, and Latin America (see Chapter 106).[49] Acutely, there may be tender hepatomegaly and anorexia. The diagnosis is suggested by peripheral blood eosinophilia and confirmed by demonstration of worms and eggs in the liver by biopsy or at autopsy. Hepatomegaly in acute schistosomiasis results from egg deposition in the liver and the immune response to worm and egg antigens (see Chapter 116).[50] Specific serologic tests become positive several weeks before eggs can be found in the stool.

CHRONIC HEPATITIS AND OTHER CAUSES OF DIFFUSE HEPATOMEGALY

Chronic active hepatitis in the tropics is caused most commonly by HBV and HCV (see Chapter 64). Co-infection with HDV may accelerate the course of chronic HBV infection. While failure to resolve infection with these agents may lead to cirrhosis or hepatoma, persons with chronic hepatitis may remain asymptomatic for years, despite persistently elevated hepatic enzymes. Serologic testing and liver biopsy confirm the diagnosis.

Macronodular or "postnecrotic" cirrhosis develops in up to 25% of chronic hepatitis B surface antigen carriers and in over 20% of persons infected with HCV for over 20 years. The process may be clinically silent for several years before the appearance of symptoms and signs of hepatocellular dysfunction and portal hypertension such as jaundice, encephalopathy, ascites, and bleeding from esophageal varices. The liver is firm, nodular, and shrunken.

The periportal or "pipe stem" fibrosis of chronic schistosomiasis gives the liver a nodular appearance which resembles that of cirrhosis. True cirrhosis in schistosomiasis, however, is usually due to coinfection with HBV or HCV, or other chronic liver disease, and only occasionally is it seen in the absence of other hepatic lesions.[51] Cirrhosis has been reported as a consequence of visceral leishmaniasis.

Chronic alcoholism is a common cause of micronodular cirrhosis in the tropics. African or Bantu cirrhosis is thought to be related in part to chronic iron overload and hemochromatosis, whereas Indian childhood cirrhosis may be related to high copper intake as well as genetic factors.[52] Many cases of cirrhosis in the tropics remain undiagnosed. The differential diagnosis of hepatomegaly is shown in Box 127-1.

Granulomatous Disease

Systemic infections may infiltrate the liver and induce granuloma formation. Usually, both the liver and spleen are enlarged, and the alkaline phosphatase is elevated. In visceral leishmaniasis, disseminated tuberculosis, atypical mycobacterial infections, histoplasmosis, disseminated *Penicillium marneffei* infection, and other fungal infections, organisms invade Kupffer cells and other cells of the reticuloendothelial system. Disseminated infections of this sort are common in advanced human immunodeficiency virus (HIV) disease, but because of impaired immunity there may be little or no granulomatous reaction on histologic examination. Diagnosis is made by microscopic examination of biopsied liver tissue and culture of tissue and blood.

In chronic schistosomiasis mansoni and schistosomiasis japonica, granulomas form around eggs trapped in portal venules. Typically, the left lobe of the liver is enlarged more than the right lobe. As infection progresses, the size of the liver decreases as the diameter of the granulomas is reduced by immunomodulation. Periportal fibrosis, a specific finding in hepatosplenic schistosomiasis, is detected by US, CT, and MRI. In *Schistosoma japonicum* infection, calcified eggs in the liver

Box 127-1 Differential Diagnosis of Hepatomegaly

Infiltrating or Granulomatous Infections
Q fever
Melioidosis
Psittacosis
Brucellosis
Granuloma inguinale
Tularemia
Listeriosis
Syphilis
Bartonellosis
Tuberculosis
BCG vaccination or immunotherapy
Leprosy
Cryptococcosis
Histoplasmosis and other endemic fungi
Visceral leishmaniasis
Schistosomiasis
Microsporidiosis
Strongyloidiasis
Ascariasis
Toxocariasis
Capillariasis
Baylisascaris infection
Fascioliasis
Viral infections (CMV, EBV)

Abscesses and Cysts
See Figure 127-3

Response to Systemic Infection
See Figure 127-1

Acute Hepatitis
See Figure 127-1

Portal Hypertension
Schistosomiasis
Cirrhosis
Chronic liver disease
Portal vein thrombosis
Veno-occlusive disease
Noncirrhotic portal fibrosis
Clonorchiasis

Noninfectious Causes
Lymphoma
Leukemia
Metastatic carcinoma
Hepatocellular carcinoma
Fatty changes
Polycystic disease
Heart failure
Amyloidosis
Alcoholic cirrhosis
Siderosis and septal fibrosis
Bantu cirrhosis

BCG, bacille Calmette-Guérin; CMV, cytomegalovirus; EBV, Epstein-Barr virus

produce a characteristic "turtle-back" pattern on MRI. In severe cases, portal hypertension may lead to gastroesophageal varices, but jaundice, ascites, and hepatic encephalopathy are only seen in "decompensated" cases in which there is hepatocellular damage as well as portal hypertension. The diagnosis of chronic schistosomiasis is made by finding eggs in specimens of stool. Serologic tests are useful for screening travelers, who often have light and asymptomatic infections. Hepatosplenomegaly and early periportal fibrosis may regress after treatment with praziquantel.

Granulomas may form around migrating filariform larvae of *Strongyloides* during hyperinfection and dissemination. Granulomas form around *Ascaris* eggs trapped in liver tissue when adult worms enter the biliary tree. Hepatic granulomas around adult worms, larvae, and eggs are characteristic of chronic *Capillaria hepatica* infection. In visceral larva migrans due to *Toxocara canis* or *Baylisascaris procyonis,* migrating larvae provoke an eosinophilic granulomatous response.[53] Hepatomegaly, fever, and peripheral blood eosinophilia prompt a clinical diagnosis, which can be confirmed by serologic tests.

Space-Occupying Lesions of the Liver

Symptoms of mass lesions in the liver produce abdominal discomfort from distention of Glisson's capsule, an increase in abdominal girth, obstruction of the biliary system, or rupture into the peritoneum, pericardium, or pleural space or through the abdominal wall. Asymptomatic lesions occasionally are detected by imaging procedures during evaluation of unexplained fever or weight loss. The characteristics of lesions imaged by US, CT, or MRI may yield a precise diagnosis of certain helminthic infections such as schistosomiasis, acute fascioliasis, or echinococcosis, but the cause of most lesions is determined by serologic tests, blood cultures, or culture and microscopic examination of specimens obtained by aspiration or biopsy.

Liver abscesses, whether amebic or bacterial, may present subacutely with low-grade fever, weight loss, and localized pain, or acutely with temperatures above 102°F and signs of toxicity. Jaundice is unusual in the absence of biliary obstruction, and the alkaline phosphatase may be the only hepatic enzyme that is elevated.

Certain features may help differentiate amebic and bacterial abscesses[54] (Fig. 127-2). Amebic abscesses occur frequently in Mexico, Central America, northern South America, West and South Africa, and India. Most persons with amebic abscesses do not have dysentery, and stool examination does not show trophozoites or cysts in 50% of those tested. Serologic tests for antiamebic antibodies become positive in 99% of persons after 7 days of symptoms. Antibodies may persist for years, however, and the specificity of serologic tests may be low in endemic areas. Aspiration of the abscess usually is not necessary for diagnosis; abscess fluid typically contains few or no amebae, rare white blood cells, and no bacteria. A trial of metronidazole or tinidazole confirms a clinical diagnosis if patients defervesce or show symptomatic improvement within a few days.[55] Aspiration is indicated in cases of pending rupture or in cases with uncertain diagnoses that do not respond to medical treatment.[56] Treatment with metronidazole or tinidazole should be followed by a course of a luminal amebicide such as paromomycin, iodoquinol, or diloxanide furoate.

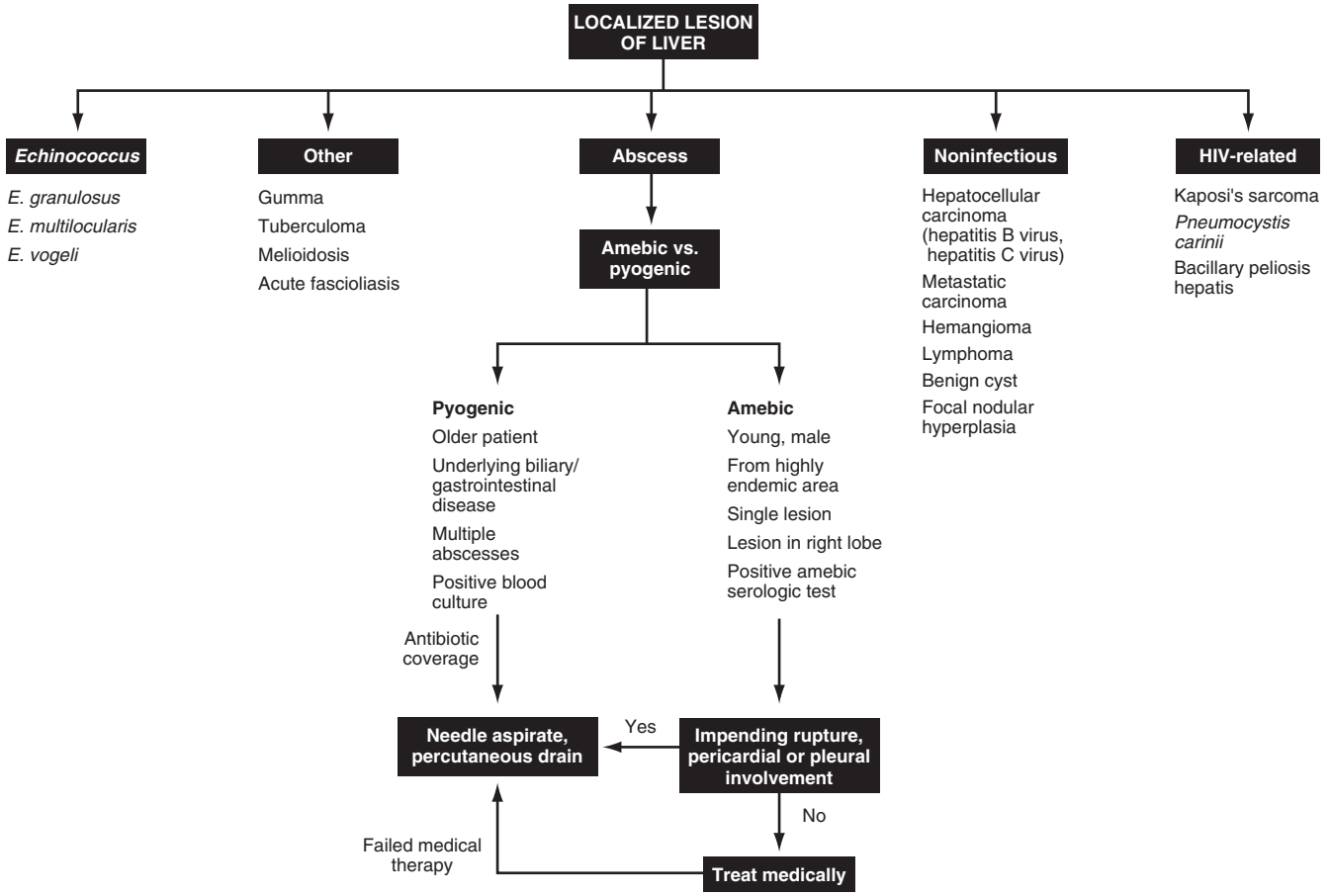

FIGURE 127-2 Differential diagnosis of space-occupying lesions of the liver.

Pyogenic liver abscesses most commonly are caused by enteric organisms, streptococci, and *Staphylococcus aureus*.[57] Blood cultures and cultures of abscess fluid are positive in about 50% and 73% of persons, respectively.[58] In the tropics, *Salmonella typhi, Brucella* species, and *Burkholderia (Pseudomonas) pseudomallei* occasionally cause hepatic abscesses. Occasional causes of large space-occupying lesions in the liver include tuberculosis, gummatous syphilis, and, in persons with AIDS, bartonellosis (peliosis hepatis), and *Pneumocystis jiroveciii*. During acute fascioliasis, CT or MR often show hypodense lesions in the liver measuring 1 cm or more in diameter that move to different parts of the liver over the course of several weeks. These lesions correspond to the tortuous and branching linear tracks of necrotic tissue and eosinophilic inflammatory infiltrates along the path of larval migration.[59]

Hydatid cysts of the liver (see Chapter 114) may be distinguished from simple hepatic cysts when US, CT, or MRI shows intracystic septations indicative of daughter cysts. Otherwise, a history of residence in a sheep raising or other endemic area or a history of urticarial or anaphylactic reactions may suggest the diagnosis of hydatid disease. A highly sensitive enzyme-linked immunosorbent assay (ELISA) and confirmatory immunoblot for antibodies to *Echinococcus granulosus* are available.[60] Microscopic examination of cyst fluid taken by needle aspiration or at surgery usually shows diagnostic protoscolices, hooklets, and calcareous bodies.[61] Treatment includes high-dose albendazole and either careful surgery or percutaneous drainage with inactivation of cysts.[62,63] Less common cestodes that cause mass lesions in the liver include *Echinococcus multilocularis* in northern regions of the world and *Echinococcus vogeli* and *Echinococcus oligarthrus* in Central and South America.[64] Hepatic cysticercosis is unusual.

Vascular Disease

Chronic passive congestion of the liver due to heart failure may produce chronic hepatomegaly and eventually cardiac cirrhosis. In tropical areas, important causes include chronic Chagas' cardiomyopathy, rheumatic heart disease, restrictive pericarditis from tuberculosis, and endomyocardial fibrosis. Veno-occlusive disease involving hepatic venules causes rapidly progressive tender hepatomegaly, ascites, and death from variceal bleeding or liver failure. It is associated with ingestion of pyrrolizidine alkaloids in herbal teas in Jamaica and parts of Africa and Asia.[65]

Splenomegaly

The spleen is enlarged in many of the same infections in which the liver is enlarged (Box 127-2). Massive splenomegaly may be seen in visceral leishmaniasis, chronic

Box 127-2 Differential Diagnosis of Splenomegaly*

Infiltrating or Granulomatous Infections
Visceral leishmaniasis
Tuberculosis
Viral infection
Fungal infection

Abscesses and Cysts
Brucellosis
Salmonellosis
Other bacterial abscesses
Echinococcosis
Melioidosis

Response to Systemic Infection
Malaria
Acute Chagas' disease
African trypanosomiasis
Endocarditis
Typhus
Bartonellosis
Rickettsial disease
Viral disease
Salmonellosis

Portal Hypertension
Schistosomiasis
Cirrhosis
Chronic liver disease
Portal vein thrombosis
Veno-occlusive disease
Noncirrhotic portal fibrosis
Clonorchiasis

Noninfectious Causes
Lymphoma
Leukemia
Metastatic carcinoma
Sickle cell disease
Thalassemia
Thrombocytopenic purpura
Felty's syndrome
Heart failure
Amyloidosis

*Many of the infectious diseases listed in Box 127-1 can also cause splenomegaly.

malaria (tropical splenomegaly syndrome), and myeloproliferative disorders.[66] Splenomegaly secondary to portal hypertension occurs with schistosomiasis, cirrhosis, and many other severe chronic liver diseases. Unusual causes of splenomegaly in the tropics include abscesses due to *Salmonella typhi, Brucella* species (especially *B. suis*), and *Burkholderia (Pseudomonas) pseudomallei*. Hypoechogenic lesions in the spleen have been detected by ultrasonography in persons with loiasis.[67]

JAUNDICE

Tropical infectious diseases produce jaundice by several mechanisms (Fig. 127-3). Hemolysis leading to predominantly unconjugated hyperbilirubinemia and depressed serum haptoglobin levels is the result of direct infection of red blood cells by *Plasmodia, Babesia,* and *Bartonella bacilliformis.* It also may occur via indirect mechanisms such as disseminated intravascular coagulation accompanying a variety of systemic infections or the hemolytic-uremic syndrome associated with *Escherichia coli* O157-H7. Mixed conjugated and unconjugated hyperbilirubinemia is seen with infections that produce hepatitis by directly or indirectly damaging hepatocytes, as discussed earlier. Typically, there is an element of intrahepatic cholestasis in addition to impaired uptake and conjugation of bilirubin.

Obstruction of biliary ducts by stones, tumors, strictures, and certain infections produces marked elevation of the serum conjugated bilirubin and serum alkaline phosphatase, 5-nucleotidase, and γ-glutamyltranspeptidase. US, CT, and endoscopic cholangiography assist in the identification of the cause of obstruction.

BILIARY OBSTRUCTION

Obstruction of the biliary or cystic duct leads to biliary colic with right upper quadrant pain or pressure of sudden onset that radiates to the shoulder (Table 127-1). Persistence and progression of the pain, frequently with nausea, vomiting, localized peritoneal signs, and low-grade fever suggest cholecystitis. High fevers, shaking chills, leukocytosis, and jaundice suggest cholangitis, which may lead to septicemia and shock. Gradual obstruction of the common bile duct leads to painless jaundice, often with pruritus.

Obstruction of the biliary tract in the tropics is frequently caused by parasitic infections. Biliary ascariasis (see Chapter 109)

Table 127-1 Causes of Obstructive Biliary Disease in the Tropics

Infectious	Noninfectious
Leptospirosis	Neoplasma
Salmonellosis	Metastatic disease
Tuberculosis	Hepatoma
Syphilis	Cholangiocarcinoma associated with *Clonorchis* or *Opisthorchis* infection
Actinomycosis	Pancreatitis
Helminthic infections	Lymphadenopathy
Nematodes	Gallstones
Ascaris lumbricoides	
Strongyloides stercoralis	
Capillaria hepatica	
Cestodes	
Echinococcus spp.	
Trematodes	
Clonorchis sinensis	
Opisthorchis viverrini	
Opisthorchis felineus	
Fasciola hepatica	
Fasciola gigantica	
Paragonimus spp.	
Protozoa	
Cryptosporidium parvum	
Isospora belli	
Cyclospora cayetanensis	
Giardia lamblia	
Microsporidia	

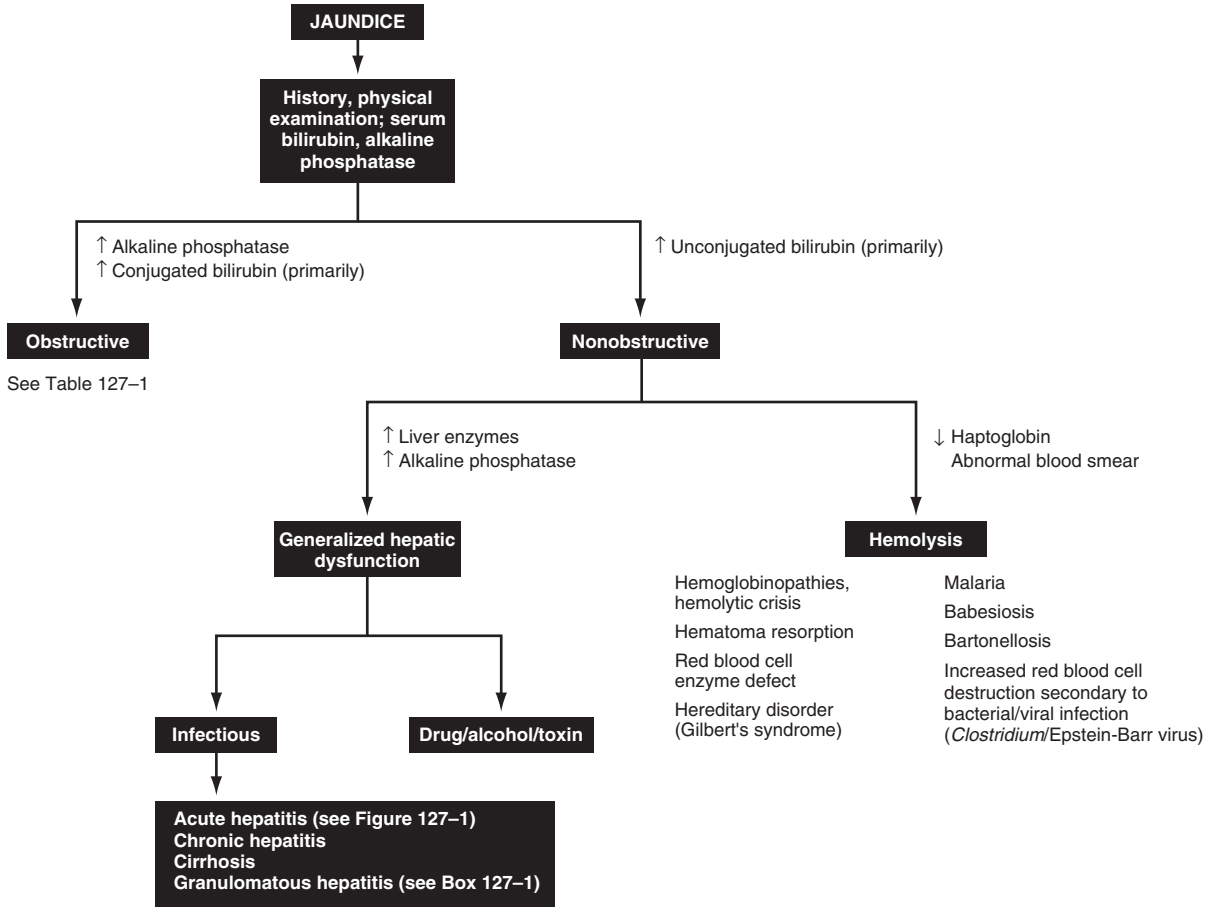

FIGURE 127-3 Differential diagnosis and evaluation of jaundice.

complicates chronic ascariasis in fewer than 0.1% of cases, but the huge number of infected persons makes the condition an important cause of hepatobiliary disease.[11] When individual adult worms enter and exit the bile ducts, symptoms of biliary colic are intermittent, but when worms fail to exit the duct, pyogenic cholangitis, hemorrhagic pancreatitis, or liver abscesses may result. Worms that die in the biliary tree may form the nidus of gallstones.[68] In a series of 500 patients with biliary and pancreatic ascariasis in India, 56% had biliary colic, 24% had acute cholangitis, 13% had acute cholecystitis, 6% had pancreatitis, and 1% had liver abscesses.[14] The diagnosis is made by US, CT, cholangiography, or endoscopic retrograde cholangiopancreatography (ERCP) and may demonstrate worms in the biliary or pancreatic ducts or gallbladder.[69,70] Treatment consists of extraction of worms during ERCP or anthelmintic treatment, preferably with pyrantel pamoate, which acts rapidly and paralyzes the worms. Nasogastric suction, antispasmodics, analgesics, and intravenous fluids usually obviate the need for surgery.

Clonorchiasis and opisthorchiasis (see Chapter 117) are common infections in Southeast Asia, China, and other parts of Asia where carp is consumed without proper cooking.[71,72] Most persons are asymptomatic, but small numbers of persons with long-standing infection develop recurrent episodes of cholangitis or cholangiocarcinoma.[73] Adult flukes that inhabit the bile ducts and gallbladder are responsible for hyperplasia of the ductal epithelium and occasionally biliary stones or pancreatitis. Chronic infections with adult *Fasciola hepatica* and *Fasciola gigantica* may remain asymptomatic for years before adult worms cause cholecystitis and cholangitis.[74] Hemobilia from ulceration of biliary epithelium, sclerosing cholangitis, and biliary stones are unusual complications of chronic fascioliasis.[75] The diagnosis of chronic clonorchiasis, opisthorchiasis, and fascioliasis is made by identifying eggs in the stool or bile or identifying adult worms by cholangiography or visually at the time of surgery. US and CT may demonstrate adult *Fasciola. Paragonimus* has been reported to cause obstructive granulomas involving the biliary tree resulting in biliary cirrhosis (see Chapter 117).[76]

Hydatid cysts of the liver (see Chapter 114) cause biliary obstruction by compressing biliary radicals as they grow or by rupturing into the biliary tree and causing blockage with daughter cysts and cyst membranes.[77] Cyst rupture can be provoked by trauma and may lead to bacterial cholangitis, liver abscess, and anaphylactic reactions to the highly antigenic cyst contents.

Other parasitic causes of biliary diseases include *Cryptosporidium parvum* (see Chapter 88) and microsporidia (see Chapter 96) in persons with AIDS. Findings are similar to those of primary sclerosing cholangitis, with diffuse involvement of intrahepatic or extrahepatic bile ducts, or both, strictures, ampullary stenosis, and pancreatic duct involvement.

ERCP defines the lesions anatomically, and examination of feces or bile for oocysts of cryptosporidia or *Isospora* or spores of microsporidia are diagnostic. AIDS-associated cholangiopathy may also be caused by cytomegalovirus, *Mycobacterium avium* complex, *Mycobacterium tuberculosis,* and *Histoplasma capsulatum.*[78–81]

Acalculous cholecystitis may be provoked by organisms that infect the gallbladder in the absence of stones. Leptospirosis, salmonellosis, and giardiasis have been implicated in immunocompetent persons, and the same agents that cause AIDS-associated cholangiopathy occasionally cause acalculous cholecystitis in HIV-infected persons. Acalculous cholecystitis has been seen in association with systemic infections such as actinomycosis, tuberculosis, and syphilis.

Cholelithiasis has become more common in some developing areas as residents have adopted a westernized diet.[1] In addition, gallstones result from chronic hemolytic states such as sickle cell anemia and other hemoglobinopathies and malaria. Recurrent pyogenic cholangitis is a condition of unknown cause in the Far East in which there is formation of pigment stones and sludge. It has been suggested that parasites such as *Clonorchis, Opisthorchis,* and *Ascaris* act as the nidus for stone formation in this condition, but dietary deficiencies that alter bile salt metabolism may be more important.

HIV INFECTION AND HEPATOBILIARY DISEASE

HIV infection, which is highly prevalent in many parts of the tropics (see Chapters 76 and 133), may alter the natural history, clinical presentation, diagnosis, and management of infections involving the liver and biliary tract. For example, HIV infection may lead to unusual clinical syndromes, such as cholangitis caused by cytomegalovirus, intestinal coccidia, microsporidia, and mycobacteria, or bacterial peliosis due to *Bartonella*. HIV co-infection has been associated with decreased egg excretion in persons with *S. mansoni* due to impaired granuloma formation and increased trapping of eggs in tissue. Serologic tests for the diagnosis of visceral leishmaniasis may yield false negative results in HIV-infected patients, but recovery of parasites from the peripheral blood is enhanced. Treatment of certain infections of the hepatobiliary tract in persons infected with HIV may present difficult challenges, such as the high rate of relapse of visceral leishmaniasis following standard therapy. Importantly, highly active antiretroviral therapy (HAART) may play a key role in preventing progression of latent diseases, reducing the rate of relapse, and enhancing efficacy of treatment.[82,83]

REFERENCES

1. Cook GC: Gastroenterological emergencies in the tropics. Baillieres Clin Gastroenterol 5:861–886, 1991.
2. Gyr KE, Barz A: Imported gastrointestinal diseases in industrialized nations. Baillieres Clin Gastroenterol 1:425–445, 1987.
3. Steffen R, Rickenbach M, Wilhelm U, et al: Health problems after travel to developing countries. J Infect Dis 156:84–91, 1987.
4. Wilson M: World Guide to Infections: Diseases, Distribution, Diagnosis. Oxford, Oxford University Press, 1991.
5. Keystone J, Kozarsky P, Freedman D, et al: Travel Medicine. Philadelphia, CV Mosby, 2003.
6. Liu LX, Weller PF: Approach to the febrile traveler returning from Southeast Asia and Oceania. Curr Clin Top Infect Dis 12:138–164, 1992.
7. Wyler DJ: Evaluation of cryptic fever in a traveler to Africa. Curr Clin Top Infect Dis 12:329–347, 1992.
8. Oster CN, Tramont EC: Fever in a recent visitor to the Middle East. Curr Clin Top Infect Dis 13:57–73, 1993.
9. Maguire JH: Epidemiologic considerations in the evaluation of undifferentiated fever in a traveler returning from Latin America or the Caribbean. Curr Clin Top Infect Dis 13:26–56, 1993.
10. Gust ID, Ruff TA: Hepatitis in the tropics. Med J Aust 159:691–695, 1993.
11. Crompton DWT, Nesheim MC, Pawlowski ZS (eds): Ascariasis and Its Prevention and Control. London, Taylor & Francis, 1989.
12. Pawlowski Z: Ascariasis. Clin Trop Med Common Dis 2:595, 1987.
13. Schuster DI, Belin RP, Parker JC Jr, et al: Ascariasis—Its complications, unusual presentations and surgical approaches. South Med J 70:176–178, 1977.
14. Khuroo MS, Zargar SA, Mahajan R: Hepatobiliary and pancreatic ascariasis in India. Lancet 335:1503–1506, 1990.
15. el-Tahir MI, Omojola MF, Malatani T, et al: Hydatid disease of the liver: Evaluation of ultrasound and computed tomography. Br J Radiol 65:390–392, 1992.
16. Takeyama N, Okumura N, Sakai Y, et al: Computed tomography findings of hepatic lesions in human fascioliasis: Report of two cases. Am J Gastroenterol 81:1078–1081, 1986.
17. Richter J, Hatz C, Haussinger D: Ultrasound in tropical and parasitic diseases. Lancet 362:900–902, 2003.
18. Gilles HM, Warrell DA, Bruce-Chwatt, LJ: Bruce-Chwatt's Essential Malariology, 3rd ed. London, Edward Arnold, 1993.
19. Abdool Karim SS, Coutsoudis A: Sero-epidemiology of hepatitis A in black South African children. S Afr Med J 83:748–750, 1993.
20. Innis BL, Snitbhan R, Hoke CH, et al: The declining transmission of hepatitis A in Thailand. J Infect Dis 163:989–995, 1991.
21. Steffen R: Risk of hepatitis A in travellers. Vaccine 10(suppl 1): S69–S72, 1992.
22. Koff RS: Preventing hepatitis A infections in travelers to endemic areas. Am J Trop Med Hyg 53:586–590, 1995.
23. Perrillo RP: Hepatitis B: Transmission and natural history. Gut 34:S48–S49, 1993.
24. Moyer LA, Mast EE: Hepatitis B: Virology, epidemiology, disease, and prevention, and an overview of viral hepatitis. Am J Prev Med 10(suppl):45–55, 1994.
25. Steffen R: Risks of hepatitis B for travellers. Vaccine 8(suppl):S31–S32; discussion S41–S43, 1990.
26. Struve J, Norrbohm O, Stenbeck J, et al: Risk factors for hepatitis A, B and C virus infection among Swedish expatriates. J Infect 31:205–209, 1995.
27. Buitrago B, Hadler SC, Popper H, et al: Epidemiologic aspects of Santa Marta hepatitis over a 40-year period. Hepatology 6:1292–1296, 1986.
28. Hadler SC, De Monzon M, Ponzetto A, et al: Delta virus infection and severe hepatitis. An epidemic in the Yucpa Indians of Venezuela. Ann Intern Med 100:339–344, 1984.
29. Bensabath G, Hadler SC, Soares MC, et al: Hepatitis delta virus infection and Lábrea hepatitis. Prevalence and role in fulminant hepatitis in the Amazon Basin. JAMA 258:479–483, 1987.
30. Sharara AI: Chronic hepatitis C. South Med J 90:872–877, 1997.
31. Tibbs CJ: Tropical aspects of viral hepatitis. Hepatitis C. Trans R Soc Trop Med Hyg 91:121–124, 1997.
32. Ray Kim W: Global epidemiology and burden of hepatitis C. Microbes Infect 4:1219–1225, 2002.
33. Rao MR, Naficy AB, Darwish MA, et al: Further evidence for association of hepatitis C infection with parenteral schistosomiasis treatment in Egypt. BMC Infect Dis 2:29, 2002.
34. Bader TF, Krawczynski K, Polish LB, et al: Hepatitis E in a U.S. traveler to Mexico. N Engl J Med 325:1659, 1991.
35. Centers for Disease Control and Prevention: Hepatitis E among US travelers, 1989–1992. JAMA 269:845–846, 1993.
36. Emerson SU, Purcell RH: Hepatitis E virus. Rev Med Virol 13:145–154, 2003.
37. DeGuzman LJ, Pitrak DL, Dawson GJ, et al: Diagnosis of acute hepatitis E infection utilizing enzyme immunoassay. Dig Dis Sci 39:1691–1693, 1994.
38. Kumar S, Pound DC: Serologic diagnosis of viral hepatitis. Postgrad Med 92:55–62, 65, 68, 1992.
39. Teichmann D, Gobels K, Niedrig M, et al: Dengue virus infection in travellers returning to Berlin, Germany: Clinical, laboratory, and diagnostic aspects. Acta Trop 90:87–95, 2004.

40. Speed BR, Gerrard MP, Kennett ML, et al: Viral haemorrhagic fevers: Current status, future threats. Med J Aust 164:79–83, 1996.
41. Chau TN, Lee KC, Yao H, et al: SARS-associated viral hepatitis caused by a novel coronavirus: Report of three cases. Hepatology 39:302–310, 2004.
42. van Crevel R, Speelman P, Gravekamp C, et al: Leptospirosis in travelers. Clin Infect Dis 19:132–134, 1994.
43. Sejvar J, Bancroft E, Winthrop K, et al: Leptospirosis in "Eco-Challenge" athletes, Malaysian Borneo, 2000. Emerg Infect Dis 9:702–707, 2003.
44. Zaidi SA, Singer C: Gastrointestinal and hepatic manifestations of tickborne diseases in the United States. Clin Infect Dis 34:1206–1212, 2002.
45. Memish ZA, Balkhy HH: Brucellosis and international travel. J Travel Med 11:49–55, 2004.
46. Asada Y, Hayashi T, Sumiyoshi A, et al: Miliary tuberculosis presenting as fever and jaundice with hepatic failure. Hum Pathol 22:92–94, 1991.
47. Han JK, Choi BI, Cho JM, et al: Radiological findings of human fascioliasis. Abdom Imaging 18:261–264, 1993.
48. Hillyer GV, Soler de Galanes M: Initial feasibility studies of the fast-ELISA for the immunodiagnosis of fascioliasis. J Parasitol 77:362–365, 1991.
49. Guttierrez Y: Diagnostic Pathology of Parasitic Infections with Clinical Correlations. New York, Oxford University Press, 2000.
50. Lambertucci JR: A new approach to the treatment of acute schistosomiasis. Mem Inst Oswaldo Cruz 84(suppl 1):23–30, 1989.
51. Lichtenberg V: Consequences of infections with schistosomes. In Rollinson D, Simpson AJG (eds): Biology of Schistosomes from Genes to Latrines. London, Academic Press, 1987, p 185.
52. Scheinberg IH, Sternlieb I: Is non-Indian childhood cirrhosis caused by excess dietary copper? Lancet 344:1002–1004, 1994.
53. Glickman LT, Magnaval JF: Zoonotic roundworm infections. Infect Dis Clin North Am 7:717–732, 1993.
54. Barnes PF, De Cock KM, Reynolds TN, et al: A comparison of amebic and pyogenic abscess of the liver. Medicine (Baltimore) 66:472–483, 1987.
55. Sharma MP, Rai RR, Acharya SK, et al: Needle aspiration of amoebic liver abscess. BMJ 299:1308–1309, 1989.
56. Singh JP, Kashyap A: A comparative evaluation of percutaneous catheter drainage for resistant amebic liver abscesses. Am J Surg 158:58–62, 1989.
57. Rubin RH, Swartz MN, Malt R: Hepatic abscess: Changes in clinical, bacteriologic and therapeutic aspects. Am J Med 57:601–610, 1974.
58. McDonald MI, Corey GR, Gallis HA, et al: Single and multiple pyogenic liver abscesses. Natural history, diagnosis and treatment, with emphasis on percutaneous drainage. Medicine (Baltimore) 63:291–302, 1984.
59. MacLean JD, Graeme-Cook FM: Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 12–2002. A 50-year-old man with eosinophilia and fluctuating hepatic lesions. N Engl J Med 346:1232–1239, 2002.
60. Donovan SM, Mickiewicz N, Meyer RD, et al: Imported echinococcosis in southern California. Am J Trop Med Hyg 53:668–671, 1995.
61. Filice C, Di Perri G, Strosselli M, et al: Parasitologic findings in percutaneous drainage of human hydatid liver cysts. J Infect Dis 161:1290–1295, 1990.
62. Bret PM, Fond A, Bretagnolle M, et al: Percutaneous aspiration and drainage of hydatid cysts in the liver. Radiology 168:617–620, 1988.
63. Filice C, Brunetti E, Bruno R, et al: Percutaneous drainage of echinococcal cysts (PAIR—puncture, aspiration, injection, reaspiration): Results of a worldwide survey for assessment of its safety and efficacy. WHO-Informal Working Group on Echinococcosis-Pair Network. Gut 47:156–157, 2000.
64. Kammerer WS, Schantz PM: Echinococcal disease. Infect Dis Clin North Am 7:605–618, 1993.
65. MacGregor FB, Abernethy VE, Dahabra S, et al: Hepatotoxicity of herbal remedies. BMJ 299:1156–1157, 1989.
66. Hutt MS, Lowenthal MN: Chronic splenomegaly in the tropics. Trop Doct 4:51–55, 1974.
67. Schuurkamp GJ, Kereu RK, Bulungol PK, et al: Diethylcarbamazine in the control of splenomegaly associated with *Bancroftian filariasis* in the Ok Tedi area of Papua New Guinea. Trans R Soc Trop Med Hyg 86:531–536, 1992.
68. Pilankar KS, Amarapurkar AD, Joshi RM, et al: Hepatolithiasis with biliary ascariasis—A case report. BMC Gastroenterol 3:35, 2003.
69. Filice C, Marchi L, Meloni C, et al: Ultrasound in the diagnosis of gallbladder ascariasis. Abdom Imaging 20:320–322, 1995.
70. Rocha Mde S, Costa NS, Costa JC, et al: CT identification of ascaris in the biliary tract. Abdom Imaging 20:317–319, 1995.
71. Mairiang E, Mairiang P: Clinical manifestation of opisthorchiasis and treatment. Acta Trop 88:221–227, 2003.
72. Chan HH, Lai KH, Lo GH, et al: The clinical and cholangiographic picture of hepatic clonorchiasis. J Clin Gastroenterol 34:183–186, 2002.
73. Sithithaworn P, Haswell-Elkins MR, Mairiang P, et al: Parasite-associated morbidity: Liver fluke infection and bile duct cancer in northeast Thailand. Int J Parasitol 24:833–843, 1994.
74. Harinasuta T, Pungpak S, Keystone JS: Trematode infections. Opisthorchiasis, clonorchiasis, fascioliasis, and paragonimiasis. Infect Dis Clin North Am 7:699–716, 1993.
75. Acuna-Soto R, Braun-Roth G: Bleeding ulcer in the common bile duct due to *Fasciola hepatica*. Am J Gastroenterol 82:560–562, 1987.
76. Okuda K, Kuratomi S, Moriyama M, et al: Biliary cirrhosis secondary to extrapulmonary paragonimiasis. Digestion 2:347–353, 1969.
77. Atlas DH, Kamenear H: Rupture of echinococcus cysts into the bile ducts simulating stones in the common duct. Am J Med 13:384–386, 1952.
78. Morrow RH, Colebunders RL, Chin J: Interactions of HIV infection with endemic tropical diseases. AIDS 3(suppl 1):S79–S87, 1989.
79. Tarimo DS, Killewo JZ, Minjas JN, et al: Prevalence of intestinal parasites in adult patients with enteropathic AIDS in north-eastern Tanzania. East Afr Med J 73:397–399, 1996.
80. Amarapurkar DN, Chopra KB, Phadke AY, et al: Tuberculous abscess of the liver associated with HIV infection. Indian J Gastroenterol 14:21–22, 1995.
81. Houston S: Tropical respiratory medicine. 3. Histoplasmosis and pulmonary involvement in the tropics. Thorax 49:598–601, 1994.
82. de la Rosa R, Pineda JA, Delgado J, et al: Influence of highly active antiretroviral therapy on the outcome of subclinical visceral leishmaniasis in human immunodeficiency virus–infected patients. Clin Infect Dis 32:633–635, 2001.
83. Pintado V, Martin-Rabadan P, Rivera ML, et al: Visceral leishmaniasis in human immunodeficiency virus (HIV)–infected and non-HIV-infected patients. A comparative study. Medicine (Baltimore) 80:54–73, 2001.